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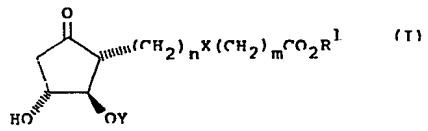
C2C

(54) Cyclopentyl ethes and their preparation and pharmaceutical formulation

(57) Compounds are described of formula (I)



(I)

in which
n is 1 or 2;
m is 2–5 and x is –CH=CH– or –CH_2–CH_2–; or m is 1–4 and x is –CH=C=CH–;
R^1 is phenyl, substituted phenyl or naphthyl;
Y substituted or unsubstituted 3-phenoxy-2-hydroxypropyl.
These compounds inhibit gastric acid secretion and provide gastrointestinal cytoprotection, and may be formulated for use in the treatment of ulcers.

GB 2 174 702 A

SPECIFICATION

Cyclopentyl ethers and their preparation and pharmaceutical formulation

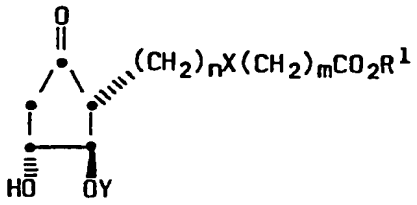
Prostaglandin E_2 is a naturally occurring substance which has many physiological actions. For example, it inhibits gastric acid secretion and provides gastrointestinal cytoprotection, lowers blood pressure, stimulates and relaxes smooth muscle, inhibits platelet aggregation and inhibits lipolysis.

Synthetic PGE_2 analogues offer the possibility of different potency, longer duration of activity and increased selectivity of action and are therefore of considerable interest.

Many different PGE_2 analogues have been suggested in the past for use in medicine but in only one instance have 13-oxa compounds been proposed in this respect. Thus, British Patent Specification 2082176A describes a group of compounds which includes 2-(heptyloxy)-3-hydroxy-5-oxo-cyclopentaneheptanoic acid and a 15-hydroxy derivative thereof. These compounds are stated to inhibit blood platelet aggregation and have bronchodilatory activity, and are proposed for use as antithrombotic or antiasthmatic agents.

We have now found a new group of cyclopentyl ethers that have PGE_2-type activity. Compounds in this class have a particularly useful profile of biological action. In particular they have shown high potency and extended duration of action as regards the inhibition of gastric acid secretion and gastrointestinal cytoprotection and are therefore of interest in the treatment of ulcers.

The invention thus provides compounds of the general formula (1)



(1)

wherein

n is 1 or 2;

m is 2–5 and X is cis or trans –CH=CH– or $-CH_2-CH_2-$; or m is 1–4 and X is –CH=C=CH–;

R^1 is

(a) phenyl [optionally substituted by C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, methylthio, methylsulphinyi, methylsulphonyl, halogen (e.g. chlorine or bromine), $-CO_2R^2$ [where R^2 is a hydrogen atom or C_{1-4} alkyl or phenyl], $-NHCOR^2$ [where R^2 is as defined above or is a phenyl group optionally substituted by hydroxyl, CH_3CONH- or

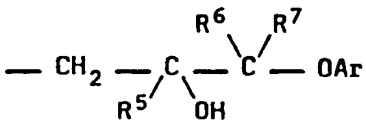
–CONH–,

$-CONR^3R^4$ [where R^3 and R^4 may be the same or different and are each a hydrogen atom or C_{1-4} alkyl group], $-NHCONH_2$, $-CH_2CH(CONH_2)NHCOCH_3$, or

$-CH_2CH(CONH_2)NHCO-$ ]

or

(b) 2-naphthyl;

Y is 

where R^5, R^6 and R^7 is each a hydrogen atom or a methyl group and at least one is a hydrogen atom; and

Ar is a phenyl group (optionally substituted by one or two C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4}alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulphinyl, C_{1-4} alkylsulphonyl, halogen or trifluoromethyl groups); and the physiologically acceptable salts thereof.

The structural formula herein are to be understood to include the enantiomers of each of the

compounds concerned as well as mixtures of the enantiomers including racemates.

In general, the compounds of formula (1) in which the carbon atom carrying the group $-(CH_2)_nX(CH_2)_mCO_2R^1$ and/or the carbon atom in the group Y carrying the –OH group (particularly the former) are in the R-configuration and mixtures containing such isomers are preferred.

The alkyl groups referred to above in the definition of the compounds of formula (1) may be straight or branched.

When R^1 in the compounds of formula (1) is phenyl substituted by a group $-CO_2H$ the compounds are capable of salt formation with bases. Examples of suitable salts are alkali metal (e.g. sodium and potassium) salts.

In compounds where X is –CH=CH– or $-CH_2CH_2-$, m is preferably 3 when n is 1, and m is preferably 2 or 4 when n is 2. When X is –CH=C=CH–, m is preferably 2 and n is 1, and 1 or 3 when n is 2.

When X is –CH=CH– it is preferably cis –CH=CH–.

When R^1 is a substituted phenyl group it may be, for example, phenyl substituted in the meta, ortho or, in particular, para positions by a chlorine or bromine atom or a methyl, ethyl propyl, n-butyl, t-butyl, methoxy, ethoxy, propoxy, butoxy, acetyl, propionyl, methylthio, methylsulphinyl, methylsulphonyl, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$,

$-CO_2-$,

–NHCHO, $-NHCOCH_3$, benzoylamino, (acetylamino)benzoylamino, (hydroxy)benzoylamino, $-CONH_2$, $-CONHCH_3$ $-CON(CH_3)_2$, $-CONHCH_3CH_3$, $-CONH(CH_2CH_3)_2$, $-NHCONH_2$, $-CH_2CH(CONH_2)NHCOCH_3$ or

$-CH_2CH(CONH_2)NHCO-$  group.

Particularly useful substituents which may be present on a substituted phenyl group R^1 include C_{1-4} alkoxy, C_{1-4} alkanoyl, methylthio, methylsulphonyl, $-CO_2R^2$, –NHCOR², –CONR³R⁴ [where R^2, R^3 and R^4 are as defined for formula (I)], $-NHCONH_2$ or $-CH_2CH(CONH_2)NHCOCH_3$ groups. Especially useful substituents of this type include methoxy, acetyl, methylthio, methylsulphonyl, $-CO_2CH_3$, $-NHCOCH_3$, benzoylamino, (p-acetylamino)benzoylamino, (p-hydroxy)benzoylamino, $-CONH_2$, $-CON(CH_3)_2$, $-NHCONH_2$ or $-CH_2CH(CONH_2)NHCOCH_3$.

The group R^1 is preferably a substituted phenyl group where the substituent may be in the meta, ortho or, in particular, para positions, or is a 2-naphthyl group.

Compounds in which R^1 is a phenyl group substituted (particularly in the para-position) by a methoxy, acetyl, $-CO_2CH_3$, $-NHCOCH_3-$, benzoylamino, $-CONH_2$, $-CON(CH_3)_2$ or $-CH_2CH(CONH_2)NHCOCH_3$ group, or R^1 is a 2-naphthyl group, are particularly useful.

In the group Y, R^6 and R^7 are preferably hydrogen atoms. Compounds in which R^5 is H or $-CH_3$ and R^6 and R^7 are hydrogen atoms are also preferred.

When the Ar phenyl group is substituted, the substituent may be in the meta, ortho or para positions and may be for example methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, butoxy, metylthio, methylsulphinyl, methylsulphonyl, fluoro, chloro, bromo or trifluoromethyl. Preferably, only a single substituent is present, particularly at the para-position. In general, Ar is preferably phenyl or phenyl substituted by halogen, particularly fluoro or chloro.

The preferences indicated above apply both separately and in combination with one or more of the other stated preferences.

A preferred group of compounds of the invention thus has the formula (1) in which:

X is –CH=CH– or $-CH_2CH_2-$ and n is 1 and m is 3 or n is 2 and m is 2 or 4, or X is –CH=C=CH– and n is 1 and m is 2 or n is 2 and m is 1 or 3;

R^1 is a phenyl group substituted (preferably in the para-position) by a methoxy, acetyl, $-CO_2CH_3$ $-NHCOCH_3$, benzoylamino, $-CONH_2$, $-CON(CH_3)_2$ or $-CH_2CH(CONH_2)NHCOCH_3$ group or R^1 is a 2-naphthyl group;

R^5 is a hydrogen atom or a methyl group;

R^6 and R^7 are hydrogen atoms; and

Ar is phenyl or phenyl substituted by fluoro or chloro.

Compounds of this type in which the carbon atom carrying the $-(CH_2)_nX(CH_2)_mCO_2R^1$ group is in the R- configuration are particularly preferred. Especially preferred compounds of this type are those in which R^1 is a phenyl group substituted (preferably in the para-position) by benzoylamino or $-CONH_2$, particularly the former.

A particularly useful group of compounds according to the invention are the following:

[1*R*-[1α(*Z*),2β(*R**),3α]]-(−)-4-Acetylphenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;

[1*R*-[1α(*Z*),2β(*R**),3α]]-(−)-4-(Acetylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;

[1*R*-[1α(*Z*),2β(*R**),3α]]-(−)-4-(Benzoylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*,*S**),2β(*R**),3α]]-(+)-4-[2-(Acetylamino)-3-amino-3-oxopropyl]phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(*R**),3α]]-(−)-(Aminocarbonyl)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(*R**),3α]]-(−)-(Benzoylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(*R**),3α]]-(−)-(N,N-Dimethylaminocarbonyl)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(*R**),3α]]-(−) Methyl 4-[[7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-1-oxo-5-heptenyl]oxy]benzoate;
[1*R*-[1α(*Z*),2β(*R**),3α]]-2-Naphthalenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β,3α]]-(−)-4-(Benzoylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-2-methyl-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β,3α]]-4-Methoxyphenyl 7-[2-[3-(4-fluorophenoxy)-2-hydroxypropoxy]-3-hydroxy-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(*R**),3α]]-(−)-4-(Benzoylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-4-heptenoate;
[1*R*-[1α,2β(*R**),3α]]-(−)-4-(Benzoylamino)phenyl 3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentaneheptanoate; and
[1*R*-[1α(*E*),2β(*R**),3α]]-(−)-4-(Aminocarbonyl)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate.

As especially useful group of compounds of this type are:
[1*R*-[1α(*Z*),2β(*R**),3α]]-(−)-4-Acetylphenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(*R**),3α]]-(−)-4-(Acetylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(*R**),3α]]-(−)-4-(Benzoylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(*R**),3α]]-(−)-4-(Aminocarbonyl)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(*R**),3α]]-(−)-3-(Benzoylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(*R**),3α]]-(−)-4-(N,N-Dimethylaminocarbonyl)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(*R**),3α]]-(−)- Methyl 4-[[7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-1-oxo-5-heptenyl]oxy]benzoate;
[1*R*-[1α(*Z*),2β,(*R**),3α]]-2-Naphthalenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β,3α]]-4-Methoxyphenyl 7-[2-[3-(4-fluorophenoxy)-2-hydroxypropoxy]-3-hydroxy-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(*R**),3α]]-(−)-4-(Benzoylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-4-heptenoate; and
[1*R*-[1α,2β(*R**),3α]]-(−)-4-(Benzoylamino)phenyl 3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentaneheptanoate.

A further important group of compounds according to the invention that have especially useful physico-chemical properties which make them very suitable for pharmaceutical formulation are:
[1*R*-[1α(*Z*),2β(*R**),3α]]-(−)-4-Acetylphenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(*R**),3α]]-(−)-4-(Acetylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(*R**),3α]]-(−)-4-(Benzoylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(*R**),3α]]-(−)-4-(Acetylamino)benzoylamino]phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(*R**),3α]]-(−)-4-(Aminocarbonyl)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*,*S**),2β(*R**),3α]]-(+)-4-[2-(Acetylamino)-3-amino-3-oxo-propyl]phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(*R**),3α]]-(−)-3-(Benzoylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(*R**),3α]]-(−) Methyl 4-[[7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-1-oxo-5-heptenyl]oxy]benzoate;

[1*R*-[1*α*(*Z*),2*β*(*R**),3*α*]]-2-(Benzoylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;

[1*R*-[1*α*(*Z*),2*β*(*R**),3*α*]]-2-Naphthalenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;

[1*R*-[1*α*(*Z*),2*β*,3*α*]]-(−)-4-(Methylsulphonyl)phenyl 7-[3-hydroxy-2-[2-hydroxy-3-[4-(methylthio)phenoxy]propoxy]-5-oxocyclopentyl]-5-heptenoate;

[1*R*-[1*α*(*Z*),2*β*(*R**),3*α*]]-(−)-4-(Benzoylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;

[1*R*-[1*α*(*Z*),2*β*(*R**),3*α*]]-(−)-4-(Benzoylamino)phenyl 9-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-7-nonenoate; and

[1*R*-[1*α*,2*β*(*R**),3*α*]]-(−)-4-(Benzoylamino)phenyl 3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentaneheptanoate.

A particularly preferred compound according to the invention is:

[1*R*-[1*α*(*Z*),2*β*(*R**),3*α*]]-(−)-4-(Benzoylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate.

Compounds of formula (1) inhibit gastric acid secretion, as determined for example by their ability to inhibit histamine-induced secretory responses in the rat perfused stomach, following the method of Ghosh M.N. and Schild in Br.J.Pharmacol., 1958, *13*, 54 as modified by Parsons M.E., Ph.D Thesis, University of London, 1969.

The compounds also provide gastrointestinal cytoprotection, as determined for example by their ability to inhibit ethanol-induced lesions in the conscious rat, following the method of Robert *et al* in Gastroenterology, 1979, *77*, 433, modified by the use of 5mg/kg/s.c. indomethacin prior to the administration of the test compound.

The compounds are thus of interest in the prevention and/or treatment of ulcers. They may also be used in the treatment of other conditions which arise from the hypersecretion of gastric acid. They may be formulated in conventional manner with one or more pharmaceutical carriers, for example for oral, buccal, parenteral or rectal administration.

The compounds may be formulated for oral administration as, for example, tablets, capsules, powders, solutions or syrups prepared by conventional means with acceptable excipents.

The compounds may be formulated for parenteral administration by bolus injections or continuous infusion. Formulations for injections may be presented in unit dosage form in ampoules, or in multi-dose containers, with an added preservative.

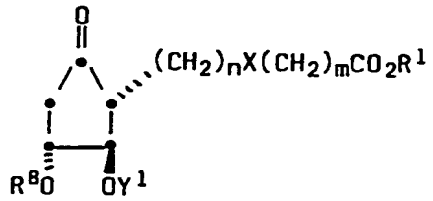
For buccal administration, the compounds may be formulated as tablets or lozenges in conventional manner; and for rectal administration compositions such as suppositories or retention enemas, for example containing conventional suppository bases such as cocoa butter or other glyceride, can be used.

The compounds are preferably administered orally, for example in amounts of 0.5 to 300 μg/kg body weight, 1 to 4 times daily. For parenteral administration, the compounds may be administered in amounts of 0.01 to 10μg/kg body weight, 1 to 4 times daily. The precise dose will of course depend on the age and condition of the patient.

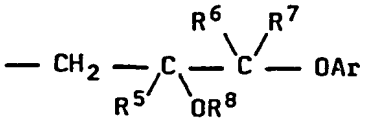
Suitable methods for preparing the compounds of the invention are described below, the various groups and symbols being as defined above except where otherwise indicated.

(a) Compounds of formula (1) may be prepared by deprotection of a corresponding compound in which the ring hydroxy group and the hydroxy group in Y are protected.

The protected compounds are thus of formula (2)



in which R^8 is a suitable hydroxyl protecting group [e.g. tetrahydropyran-2-yl, tetrahydrofuran-2-yl, ethoxyethyl, tri(hydrocarbyl)silyl or arylmethyl] and Y' is defined as a group



The two R^8 groups in the compounds of formula (2) are conveniently the same, but they may

be different if desired.

Where R^8 is tri(hydrocarbyl)silyl the hydrocarbyl substituents may be the same or different e.g. C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{7-20} aralkyl and C_{6-20} aryl groups. Such groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, allyl, phenyl and benzyl. Preferred hydrocarbyl groups are C_{1-4} alkyl, e.g. methyl and t-butyl. Trimethylsilyl and t-butyldimethylsilyl groups are particularly preferred.

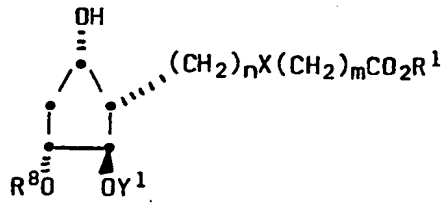
When R^8 is an arylmethyl group it may contain up to 20 carbon atoms, e.g. benzyl, diphenylmethyl or triphenylmethyl.

The method used to deprotect the protected hydroxyl group will depend on the nature of R^8 but in general acid hydrolysis or reduction may be used.

Thus, for example when R^8 is a tetrahydropyran-2-yl, tetrahydrofuran-2-yl or ethoxyethyl group deprotection may be carried out with an acid. Suitable acids include inorganic acids such as hydrochloric acid and organic acids such as acetic acid or trifluoroacetic acid. Suitable solvents include ethers (e.g. diethyl ether, dioxan and tetrahydrofuran) halogenated hydrocarbons (e.g. dichloromethane, hydrocarbons (e.g. toluene), dipolar aprotic solvents (e.g. acetone, acetonitrile, dimethylsulphoxide and dimethylformamide) and alcohols (e.g. methanol, ethanol and ethylene glycol). Where desired the solvents may be used in combination with water. The reaction may be carried out at any suitable temperature, such as from 0° to 50°C, e.g. 40° to 50°C.

A tri(hydrocarbyl)silyl group may for example be removed by acid hydrolysis, e.g. with dilute mineral acid or trifluoroacetic acid or by treatment with fluoride ions (e.g. from a quaternary ammonium fluoride such as tetra-n-butyl ammonium fluoride), or by treatment with aqueous hydrogen fluoride. Arylmethyl groups may be removed by reduction, e.g. by hydrogenolysis, e.g. with a noble metal catalyst such as platinum or palladium, or by treatment with a Lewis acid (e.g. boron trifluoride-etherate) in the presence of a thiol (e.g. ethanethiol) in a suitable solvent such as dichloromethane at e.g. room temperaure.

Compounds of formula (2) may be prepared by oxidation of a compound of formula (3)



(3)

with for example pyridinium chlorochromate in the presence of a buffer (e.g. sodium acetate) in a suitable solvent (e.g. dichloromethane) at an appropriate temperature (e.g. −10°C to room temperature). Alternatively, the oxidation may be carried out with dimethylsulphoxide, activated by N,N'-dicyclohexylcarbodiimide, in the presence of pyridinium trifluoroacetate in a solvent such as dichloromethane at e.g. −10°C to room temperature. Other conventional oxidative methods can also be used, for example Jones reagent.

Intermediate compounds of formula (3) may be prepared by the methods generally described in European Patent Specification 160495.

It will be appreciated that the deprotection method (a) is usually applied in connection with the formation by oxidation of the cyclopentyl ring oxo group. Thus, the compounds of formula (1) may generally be prepared by oxidising a corresponding compound of formula (3).

The formation of the ring oxo group may however be effected prior to the introduction of the desired R^1 group by esterification (e.g. by method (b) below) and the protecting groups removed thereafter.

(b) Compounds of formula (1) may also be prepared by esterifying the corresponding carboxylic acids, i.e. the compounds in which R^1 is a hydrogen atom, by conventional methods.

Thus for example a compound of formula (1) may be prepared by conversion of the corresponding carboxylic acid into an activated derivative (e.g. a corresponding mixed anhydride) formed for example by reaction with an alkyl chloroformate (e.g. isobutyl chloroformate) or an acid chloride (e.g. pivaloyl chloride) in the presence of a suitable base (e.g. triethylamine or pyridine). The activated derivative can then be reacted with an appropriate compound R^1OH, which are either known compounds or may be prepared by methods analogous to those used for the preparation of known compounds. Suitable solvents include dipolar aprotic solvents (e.g. acetone, acetonitrile and dimethylformamide) and halogenated hydrocarbons (e.g. dichloromethane). The reaction may be carried out at any suitable temperature e.g. from 0°C to room temperature.

The same group of compounds of formula (1) may also be prepared by first reacting the corresponding carboxylic acid with dicyclohexylcarbodiimide in the presence of 4-dimethylaminopyridine and then treating the product with a phenol R^1OH. This reaction is conveniently per-

formed at an appropriate temperature (e.g. 0°C to room temperature) in a solvent such as ether or dichloromethane.

The carboxylic acids required as starting materials for this reaction may be prepared by the methods generally described in European Patent Specification 160495.

(c) Compounds of formula (1) in which X is a $-CH_2-CH_2-$ group may be prepared by reduction of a corresponding compound in which X is a cis or trans $-CH=CH-$ group or an acetylene group. Suitable methods of reduction include hydrogen in the presence of a catalyst, e.g. palladium, on a support (e.g. carbon). Suitable solvents include ethyl acetate, ethanol and methanol.

(d) Compounds of formula (1) in which X is a $-CH=CH-$ group may be prepared by selective reduction of a corresponding compound in which X is an acetylene group. Suitable methods of reduction include hydrogen in the presence of a catalyst, e.g. palladium on a support (e.g. $CaCO_3$ or $BaSO_4$) and poisoned for example by lead or quinoline. Suitable solvents include ethyl acetate and methanol. This reaction is particularly suitable for the preparation of compounds in which X is cis $-CH=CH-$.

The acetylenes required as starting materials may be prepared from the corresponding acetylenic acids by esterification using the methods described above. The acetylenic acid intermediates may be prepared by the methods generally described in European Patent Specification 160495.

(e) Compounds of formula (1) in which X is a trans $-CH=CH-$ group may be prepared by isomerisation of a corresponding compound in which X is a cis $-CH=CH-$ group.

The isomerisation may for example be effected by treating the corresponding cis compound with toluene-p-sulphinic acid in dioxan (e.g. at reflux), or azobisisobutyronitrile and thiophenol, using for example a hydroarbon solvent (e.g. benzene) at any suitable temperature up to reflux.

The processes in methods (b–e) may also be applied to compounds of formula (2) and (3) and the products subsequently converted into compounds of formula (1) by the methods described above.

When a specific enantiomer of formula (1) is required, starting materials having the desired stereochemical configuration should be used in the above processes. Such starting materials may be prepared for example using the methods described in European Patent Specification 160495 from an enantiomeric intermediate as described in European Patent Specification 74856.

The following examples illustrate the invention.

Temperatures are in °C.

'Dried' refers to drying with anhydrous $MgSO_4$. T.l.c.—Thin layer Chromatography on silica. Chromatography was carried out on silica gel.

The following abbreviations are used:

ER-ether; EA-ethyl acetate; PE-petroleum ether (b.p. 60–80° unless otherwise stated); DIBAL-diisobutylaluminium hydride; THF-tetrahydrofuran; CH_2Cl_2-dichloromethane; $CHCl_3$-chloroform; $CHBr_3$-bromoform; DMF-dimethylformamide; DMSO-dimethylsulphoxide; EtOH-ethanol; MeOH-methanol; CH_3CN-acetonitrile; Et_3N-triethylamine; N.T.P.—normal temperature and pressure.

Intermediate 1
[1S-[1α(Z),2β(2S),3aβ5α]]-7-[5-Hydroxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoic acid*

Intermediate 2
[1S-[1α(Z),2β,3a,5α]]-(+) Methyl 7-[5-hydroxy-2-[2-methyl-3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate

Intermediate 3
(a) *[1S-[1α(Z),2β,3a,5α]]-(+)-Methyl 7-[2-[3-(4-fluorophenoxy)-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-5-hydroxy-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*

(b) *[1S-[1α(Z),2β,3a,5α]]-(+)-Methyl 7-[2-[3-(3-chlorophenoxy)-2-[(tetrahydro-2H-pyran-2-yl)oxy]-propoxy]-5-hydroxy-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*

(c) *[1S-[1α(Z),2β,3a,5α]]-(+)-Methyl 7-[5-Hydroxy-2-[3-[4-(methylthio)phenoxy]-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*

Intermediate 4
[3aR-[3aα,4α(2R),5β,6aα]]-Hexahydro-4-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-5-[(tetrahydro-2H-pyran-2-yl)oxy]-2H-cyclopenta[b]furan-2-ol*

Intermediate 5
[1R-[1α,5α,6α,8R(R*)]]-8-(2-Hydroxy-3-phenoxypropoxy)-6-(phenylmethoxy)-2-oxabicyclo[3.2.1]oc-*

tan-3-one

Intermediate 6
[1S-[1α(Z),2β(2S),3α,5α]]-(+)-Methyl 9-[5-hydroxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]-propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-7-nonenoate*

Intermediates 1–6 were prepared as described in European Patent Specification No 160495.

Intermediate 7
Methyl 4-[(tetrahydro-2H-pyran-2-yl)oxy]benzoate
A solution of methyl 4-hydroxybenzoate (10g) in EA (60ml) containing saturated ethereal HCl (3.5 ml) was treated with dihydropyran (12ml) and the solution was allowed to stand at room temperature for 24h. A further quantity of dihydropyran (12ml) and ethereal HCl (3.5ml) was added and the solution was left for 17h. The solvent was evaporated and the residue was dissolved in ER (100ml) and washed with 2N NaOH solution (2×50ml), brine (50ml) and then dried. Evaporation gave a residue which on purification by chromatography using 3:97 ER—toluene as eluant gave the *title compound* as a white solid (10.2g), m.p. 58–62°.

Intermediate 8
4-[(Tetrahydro-2H-pyran-2-yl)oxy]benzoic acid
A suspension of Intermediate 7 (10.0g) in MeOH (200ml) and 5N NaOH solution (30ml) was stirred at room temperature for 24h. The solution was evaporated to about 50ml and diluted with water (100ml). The mixture was filtered through hyflo and the filtrate was washed with ER (2×30ml) and acidified by the dropwise addition of 5N hydrochloric acid. The resulting precipitate was filtered off to give the *title compound* as a white solid (8.25g), m.p. 138–399°.

Intermediate 9
N-(4-Hydroxyphenyl)-4-[(tetrahydro-2H-pyran-2-yl)oxy]benzamide
A solution of Intermediate 8 (8.1g) in dry THF (200ml) at 0° was treated with Et_3N (6.0ml) and then pivaloyl chloride (5.4ml) and the mixture was stirred at 0° for 30 min. A solution of 4-aminophenol (3.0g) in DMF (30ml) was added and the mixture was stirred for 17h at room temperature and for 1.5h at 80°. The mixture was filtered, the filtrate was evaporated and the residue dissolved in ER (200ml). Pouring into water (200ml) gave a precipitate which was filtered off and crystallised from EA-MeOH to give the *title compound* as a white solid (5.6g), m.p. 173–174°.

Intermediate 10
(a) *[1S-[1α(Z),2β(2S*),3α,5α]]-(+)-4-Acetylphenyl 7-[5-hydroxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*
A solution of Intermediate 1 (0.45g) in dry CH_3CN (15ml) at −10° was treated with Et_3N (0.2ml) followed by isobutyl chloroformate (0.14ml). After stirring for 45 min. p-hydroxyacetophenone (0.23g) was added. Stirring was continued for 2h at −10° to 0° and then the mixture was diluted with water and extracted with ER (3×50ml). The combined extracts were washed with 10% copper sulphate solution (75ml), water (10ml) and then dried. Evaporation gave a residue which on purification by chromatography using 2:1 ER-PE (40–60°) as eluent gave the *title compound* as a gum (0.43g).
I.r. (CHB_3) 3550, 1753, 1678cm $^{-1}$, $[\alpha]_D^{22}$ +19.6° (MeOH)
The following compounds were prepared in a similar manner from Intermediate 1 and the appropriate phenol:–

(b) *[1S-[1α(Z),2β(2S*),3α,5α]]-(+)-4-(Acetylamino)phenyl 7-[5-hydroxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*
I.r. ($CHBr_3$) 3580, 3425, 1750, 1690cm $^{-1}$, $[\alpha]_D^{22}$ +7.9° (MeOH)

(c) *[1S-[1α(Z),2β(2S*),3α,5α]]-(+)-4-(Aminocarbonyl)amino]phenyl-7-[5-hydroxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*
I.r. ($CHBr_3$) 3510, 3410, 1748, 1682cm $^{-1}$, $[\alpha]_D^{22}$ +15.4° (MeOH)

(d) *[1S-[1α(Z),2β(2S*),3α,5α]]-(+)-4-(Benzoylamino)phenyl 7-[5-hydroxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*
Pivaloyl chloride (0.18g) was added to a solution of Intermediate 1 (0.7g) and Et_3N (0.38g) in dry DMF (5ml) at 0°. After 10 min a solution of 4-(benzoylamino)phenol (0.53g) in DMF (2ml) was added and stirring continued for 6h at 0° and 18h at room temperature. The reaction mixture was diluted with EA (150ml) and washed consecutively with water (2×50ml), 10% copper sulphate solution (2×50ml), water (50ml) and brine (50ml). The dried organic extract

was evaporated to give a residue which was purified by chromatography on Et_3N-deactivated silica using 1:1 cyclohexane-EA as eluent. The *title compound* was obtained as a gum (0.55g). I.r. ($CHBr_3$) 3520, 3425, 1750, 1673cm^{-1}, $[\alpha]_D^{20}$+20° ($CHCl_3$)

The following compounds were prepared in a similar manner to Intermediate 10d from Intermediate 1 and the appropriate phenol:–

(e) *[1S-[1α(Z),2β(2S*),3α,5α]]-(+)-4-(Acetylamino)benzoylamino]phenyl 7-[5-hydroxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*
I.r. ($CHBr_3$) 3580, 3520, 3425, 1745, 1690, 1670cm^{-1}, $[\alpha]_D^{20}$+20.6° ($CHCl_3$)

(f) *[1S-[1α(Z),2β(2S*),3α,5α]]-(+)-4-(Aminocarbonyl)phenyl 7-[5-hydroxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*
I.r. ($CHBr_3$) 3520, 3400, 1755, 1672cm^{-1}, $[\alpha]_D^{20}$+20° ($CHCl_3$)

(g) *[1S-[1α(Z,R*),2β(2S*),3α,5α]]-(+)-4-[2-(Acetylamino)-3-amino-3-oxopropyl]phenyl 7-[5-hydroxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*
I.r. ($CHBr_3$) 3500, 3400, 1745, 1690, 1660cm^{-1}, $[\alpha]_D^{20}$+24° ($CHCl_3$)

(h) *[1S-[1α(Z),2β(2S*),3α,5α]]-(+)-3-(Benzoylamino)phenyl 7-[5-hydroxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*
I.r. ($CHBr_3$) 3700–3100, 1755, 1677cm^{-1}, $[\alpha]_D^{20}$+27° ($CHCl_3$)

(i) *[1S-[1α(Z),2β(2S*),3α,5α]]-(+)-4-(N,N-Dimethylaminocarbonyl) phenyl 7-[5-hydroxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*
I.r. ($CHBr_3$) 3530, 1750, 1740, 1626cm^{-1}

(j) *[1S-[1α(Z),2β(2S*),3α,5α]] Methyl 4-[[7-[5-hydroxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-1-oxo-5-heptenyl]oxy]benzoate*
I.r. ($CHBr_3$) 3590, 3520, 1750, 1715cm^{-1}

(k) *[1S-[1α(Z),2β(2S*),3α,5α)-(+)-4-[[[4-[(tetrahydro-2H-pyran-2-yl)oxy]phenyl]carbonyl]amino]phenyl 7-[5-hydroxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)-oxy]cyclopentyl]-5-heptenoate*, from Intermediates 1 and 9
I.r. ($CHBr_3$) 3580, 3420, 1748, 1668cm^{-1}, $[\alpha]_D^{20}$+21° ($CHCl_3$)

(l) *[1S-[1α(Z),2β(2S*),3α,5α]]-2-(Benzoylamino)phenyl 7-[5-hydroxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*
I.r. ($CHBr_3$) 3520, 3440, 1728, 1688, 1516cm^{-1}

(m) *[1S-[1α(Z),2β(2S*),3α,5α]]-2-Naphthalenyl 7-[5-hydroxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*
I.r. ($CHBr_3$) 3530, 1750cm^{-1}

(n) *[1S-[1α(Z),2β,3α,5α]]-4-(Benzoylamino)phenyl 7-[5-hydroxy-2-[2-methyl-3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*, from Intermediate 12a.
I.r. ($CHBr_3$) 3520, 3430, 1750, 1675cm^{-1}

(o) *[1S-[1α(Z),2β,3α,5α]]-4-Methoxyphenyl 7-[2-[3-(4-fluorophenoxy)-2-[(tetrahydro-2H-pyran-2-yl)-oxy]propoxy]-5-hydroxy-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*, from Intermediate 12b. I.r. ($CHBr_3$) 3590, 3530, 1748cm^{-1}

(p) *[1S-[1α(Z),2β,3α,5α]]-4-(Methylthio)phenyl 7-[2-[3-(3-chlorophenoxy)-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-5-hydroxy-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*, from Intermediate 12c. I.r. ($CHBr_3$) 3580, 3520, 1750cm^{-1}

(q) *[1S-[1α(Z),2β,3α,5α]]-4-(Methylsulphonyl)phenyl 7-(5-hydroxy-2-[3-[4-(methylthio)phenoxy]-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*, from Intermediate 12d. I.r. ($CHBr_3$) 3520, 1758cm^{-1}

(r) *[1S-[1α,2β(2S*),3α,5α]]-4-[(Aminocarbonyl)phenyl 7-[5-hydroxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-4,5-heptadienoate*, from Intermediate 12e. I.r. ($CHBr_3$) 3520, 3405, 3600–3200, 1960, 1758, 1675cm^{-1}

(s) *[1S-[1α(Z),2β(2S*),3α,5α]]-4-(Benzoylamino)phenyl 7-[5-hydroxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*, from Intermediate 12f. I.r. ($CHBr_3$) 3520, 3430, 1750, 1678cm^{-1}

(t) *[1S-[1α(Z),2β(2S*),3α,5α]]-4-(Benzoylamino)phenyl 9-[5-hydroxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-7-nonenoate*, from Intermediate 12g. I.r. ($CHBr_3$) 3520, 3420, 1748, 1672cm^{-1}

Intermediate 11

(a) *[1R-[1α(Z),2β(2R*),3α,]]-(−)-4-Acetylphenyl 7-[5-oxo-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*
A stirred solution of Intermediate 10a (0.39g) in dry CH_2Cl_2 (4ml) and dry DMSO (0.4ml) was treated with dicyclohexylcarbodiimide (0.5g) followed by pyridinium trifluoroacetate (0.17g). After 5h at room temperature the mixture was poured into water (50ml) and extracted with ER (3× 75ml). Evaporation of the dried extracts gave a residue which was purified by chromatography on acid-washed (pH3.8) silica. The *title compound* was obtained as a colourless gum (0.27g). I.r. ($CHBr_3$) 1760, 1743, 1680cm^{-1}, $[\alpha]_D^{22.2}$ −13.7° (MeOH)

The following compound was prepared in a similar manner:–

(b) *[1R-[1α(Z),2β(2R*),3α,]]-(+)-4-(Acetylamino)phenyl 7-[5-oxo-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*, from Intermediate 10b I.r. ($CHBr_3$) 3420, 1740, 1685cm^{-1}, $[\alpha]_D^{18.6}$ +16.7° (MeOH)

(c) *[1R-[1α(Z),2β(2R*),3α,]]-4-[(Aminocarbonyl)amino]phenyl 7-[5 oxo-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*
A cold (0°), stirred suspension of Intermediate 10c (0.15g) and anhydrous sodium acetate (0.05g) in CH_2Cl_2 (2ml) was treated with pyridinium chlorochromate (0.13g). The mixture was stirred at 0° for 30 min. and at room temperature for 1h and then purified by chromatography on acid-washed (pH3.8) silica using EA as eluent. The *title compound* was obtained as a gum (0.09g). T.l.c. EA Rf 0.3.

The following compounds were prepared in a similar manner:–

(d) *[1R-[1α(Z),2β(2R*),3α,]]-(−)-4-(Benzoylamino)phenyl 7-[5-oxo-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*, from Intermediate 10d I.r. ($CHBr_3$) 3430, 1740, 1675cm^{-1}, $[\alpha]_D^{20}$ −11° ($CHCl_3$)

(e) *[1R-[1α(Z),2β(2R*),3α,]]-(−)-4-[4-(Acetylamino)benzoylamino]phenyl 7-[5-oxo-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*, from Intermediate 10e
I.r. ($CHBr_3$) 3420, 1740, 1690, 1670cm^{-1}, $[\alpha]_D^{20}$ −50 ($CHCl_3$)

(f) *[1R-[1α(Z),2β(2R*),3α,]]-(−)-4-(Aminocarbonyl)phenyl 7-[5-oxo-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*, from Intermediate 10f I.r. ($CHBr_3$) 3525, 3405, 1742, 1675, 1599cm^{-1}, $[\alpha]_D^{20}$ −16.3° ($CHCl_3$)

(g) *[1R-[1α(Z,S*),2β(2R*),3α,]]-(−)-4-[2-(Acetylamino)-3-amino-3-oxopropyl]phenyl 7-[5-oxo-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*, from Intermediate 10g.
I.r. ($CHBr_3$) 3505, 3400, 1740, 1690, 1665cm^{-1}, $[\alpha]_D^{20}$ −3.4° ($CHCl_3$)

(h) *[1R-[1α(Z),2β(2R*),3α,]]-(−)-3-(Benzoylamino)phenyl 7-[5-oxo-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*, from Intermediate 10h. I.r. ($CHBr_3$) 3430, 1742, 1680, 1526cm^{-1}, $[\alpha]_D^{20}$ −70 ($CHCl_3$)

(i) *[1R-[1α(Z),2β(2R*),3α,]]-4-(N,N-Dimethylaminocarbonyl) phenyl 7-[5-oxo-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate*, from Intermediate 10i. I.r. ($CHBr_3$) 1740, 1622cm^{-1}

(j) *[1R-[1α(Z),2β(2R*),3α,]] Methyl 4-[[7-[5-oxo-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-1-oxo-5-heptenyl]oxy]benzoate*, from Intermediate 10j. I.r. ($CHBr_3$) 1745, 1720cm^{-1}

(k) *[1R-[1α(Z),2β(2R*),3α,]]-(−)-4-[[[4-[(Tetrahydro-2H-pyran-2-yl)oxy]phenyl]carbonyl]amino]phenyl 7-[5-oxo-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]-cyclopentyl]-5-heptenoate,* from Intermediate 10k I.r. ($CHBr_3$) 3435, 1745, 1720, 1672cm^{-1} $[\alpha]_D^{20}$ −8.9° ($CHCl_3$)

11l) *[1R-[1α(Z),2β(2R*),3α,]]-2-(Benzoylamino)phenyl 7-[5-oxo-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate,* from Intermediate 10l I.r. ($CHBr_3$) 3440, 1760, 1740, 1678cm^{-1}

11m) *[1R-[1α(Z),2β(2R*),3α,]]-2-Naphthalenyl 7-[5-oxo-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)-oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate,* from Intermediate 10m I.r. ($CHBr_3$) 1745cm^{-1}

11n) *[1R-[1α(Z),2β,3α,]]-4-(Benzoylamino)phenyl 7-[2-[2-methyl-3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-5-oxo-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate,* from Intermediate 10n I.r. ($CHBr_3$) 3430, 1740, 1672cm^{-1}

11o) *[1R-[1α(Z),2β,3α,]]-4-Methoxyphenyl 7-[2-[3-(4-fluorophenoxy)-2-[(tetrahydro-2H-pyran-2-yl)-oxy]propoxy]-5-oxo-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate,* from Intermediate 10o. I.r. ($CHBr_3$) 1744cm^{-1}

The following compounds were prepared in a similar manner to Intermediate 11a:—

11p) *[1R-[1α(Z),2β,3α,]]-4-(Methylthio)phenyl 7-[2-[3-(3-chlorophenoxy)-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-5-oxo-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate,* from Intermediate 10p. I.r. ($CHBr_3$) 1742cm^{-1}

(q) *[1R-[1α(Z),2β,3α,]]-4-(Methylsulphonyl)phenyl 7-[2-[3-[4-(methylthio)phenoxy]-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-5-oxo-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoate,* from Intermediate 10q. I.r. ($CHBr_3$) 1740cm^{-1}.

The following compounds were prepared in a similar manner to Intermediate 11c:—

(r) *[1R-[1α,2β,(2R*),3α,]]-4-(Aminocarbonyl)phenyl 7-[5-oxo-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-4,5-heptadienoate,* from Intermediate 10r I.r. ($CHBr_3$) 3520, 3410, 1962, 1742, 1676cm^{-1}

(s) *[1R-[1α(Z),2β(2R*),3α,]]-4-(Benzoylamino)phenyl 7-[5-oxo-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-4-heptenoate,* from Intermediate 10s I.r. ($CHBr_3$) 3430, 1742, 1675cm^{-1}

(t) *[1R-[1α(Z),2β(2R*),3α,]]-4-(Benzoylamino)phenyl 9-[5-oxo-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-7-nonenoate,* from Intermediate 10t. I.r. ($CHBr_3$) 3430, 1742, 1678cm^{-1}.

Intermediate 12

(a) *[1S-[1α(Z),2β,3α,5α]]-7-[5-Hydroxy-2-[2-methyl-3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoic acid*

A solution of Intermediate 2 (0.98g) in MeOH (15ml) was treated with 5N NaOH solution (6ml). After 30 min the mixture was poured into water (100ml) and extracted with ER (150ml). The aqueous solution was acidified with a saturated NH_4Cl solution (150ml) and then extracted with EA (4×50ml). The combined extracts were dried and evaporated to give the *title compound* as a gum (0.88g). I.r. ($CHBr_3$) 3510, 3400–2500, 1730, 1708cm^{-1}

The following compounds were prepared in a similar manner:—

(b) *[1S[1α(Z),2β,3α,5α,]]-7-[2-[3-(4-Fluorophenoxy)-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-5-hydroxy-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoic acid,* from Intermediate 3a. I.r. ($CHBr_3$) 3510, 3400–2400, 1730, 1708cm^{-1}

(c) *[1S[1α(Z),2β,3α,5α,]]-7-[2-[3-(3-Chlorophenoxy)-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-5-hydroxy-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoic acid,* from Intermediate 3b I.r. ($CHBr_3$) 3590, 3510, 3700–2400, 1730, 1705cm^{-1}

(d) *[1S-[1α(Z),2β,3α,5α,]]-7-[5-Hydroxy-2-[3-[4-(methylthio)phenoxy]-2-[(tetrahydro-2H-pyran-2-yl)-oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-5-heptenoic acid,* from Intermediate 3c. I.r. ($CHBr_3$) 3520, 3600–2500, 1730, 1708cm^{-1}

(e) *[1S-[1α(Z),2β(2S*),3α,5α,]]-7-[5-Hydroxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-4,5-heptenoic acid*, from Intermediate 15
I.r. ($CHBr_3$) 3500, 1920, 1730cm^{-1}

(f) *[1S-[1α(Z),2β(2S*),3α,5α,]]-7-[5-Hydroxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-4-heptenoic acid*
(3-Carboxypropyl)triphenylphosphonium bromide (1.11g) and potassium *tert*-butoxide (0.58g) in dry THF (10ml) were stirred at ambient temperature for 45 min. A solution of the Intermediate 19 (0.58g) in dry THF (10ml) was added and stirring at ambient temperature was continued for 1h. A further identical quantity of preformed ylide was added to the reaction mixture and stirring was continued for 1.5h. Water (20ml) was added and the mixture was washed with ER (3×50ml). The organic washings were back extracted with 8% $NaHCO_3$ solution (2×20ml). The combined aqueous extracts were treated with saturated NH_4Cl (30ml) and the product was extracted with ER (3×50ml). The extracts were washed with brine (15ml), dried and concentrated *in vacuo* to yield the *title compound* as an oil (0.55g).
I.r. ($CHBr_3$) 3500, 3600–2300, 1728, 1710cm^{-1}

The following compound was prepared in a similar manner to Intermediate 12a:–

(g) *[1S-[1α(Z),2β(2S*),3α,5α,]]-7-[5-Hydroxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-7-nonenoic acid*, from Intermediate 6
I.r. ($CHBr_3$) 3510, 3000–2500, 1730, 1710cm^{-1}

Intermediate 13
[1S-[1α,2β(2S),3α,5α]]-Methyl 6-hydroxy-7-[5-hydroxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)-oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-4-heptynoate*
n-Butyl lithium (1.6M in hexane, 61.5ml) was added to a solution of diisopropylamine (13.8ml) and hexamethylphosphoramide (17.5ml) in ER (140ml) at 0° under nitrogen. The solution was cooled to −70° and a solution of 4-pentynoic acid (4.87g) in THF (50ml) added. The mixture was then allowed to warm to room temperature, and after 1h, a solution of Intermediate 4 (3.5g) in ER (60ml) was added. After 18h, a solution of oxalic acid dihydrate (14g) in water (200ml) was added and the organic phase separated. The aqueous phase was extracted with EA (200ml) and the combined organic phases dried and evaporated. The residue was dissolved in DMF (30ml) and treated with methyl iodide (12ml) and potassium fluoride (8g). After 3h the solution was diluted with EA (200ml) and washed with water (3×200ml) and brine (200ml). The aqueous washings were back-extracted with EA (200ml) and the combined organic phases dried and evaporated. The residue was purified by chromatography using 4:1 increasing to 2:1 ER-EA as eluent to give the *title compound* as an oil (2.9g).
I.r. ($CHBr_3$) 3580, 3500, 1728cm^{-1}

Intermediate 14
[1R-[1α,2β(2R),3α,5α]]-Methyl 6-acetyloxy-7-[5-acetyloxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-4-heptynoate*
Triethylamine (8.2ml), acetic anhydride (6.7ml) and 4-dimethylamino pyridine (70mg) were added to a stirred solution of Intermediate 13 (2.8g) in CH_2Cl_2 (60ml). After 2h the solvent was removed and chromatography of the residue using 4:1 ER-PE (40–60°) as eluent gave the *title compound* as an oil (3.1g). I.r. ($CHBr_3$) 1728cm^{-1}

Intermediate 15
[1R-[1α,2β(2R),3α,5α]]-Methyl 7-[5-acetyloxy-2-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-4,5-heptadienoate*
Methyl lithium (1.6M in ER, 44.5ml) was added to a stirred suspension of cuprous iodide (6.8g) in ER (120ml) at −10° under nitrogen. When the addition was complete, a clear solution was obtained which was then cooled to −78° and a solution of the Intermediate 14 (0.85g) in ER (50ml) at −78° was added. After 1.5h, saturated NH_4Cl solution (200ml) was added and the mixture stirred at room temperature for 1h. The organic phases was washed with saturated brine (200ml) and the aqueous phase extracted with ER (200ml). The dried organic extracts were evaporated and the residue purified by chromatography using 3:1 ER–PE (40–60°) as eluent to give the *title compound* as an oil (1.2g). I.r. ($CHBr_3$) 1960, 1728cm^{-1}

Intermediate 16
[1R-[1α,5α,6α,8R(R*)]]-8-(2-Hydroxy-3-phenoxypropoxy)-6-(phenylmethoxy)-2-oxabicyclo[3.2.1]octan-3-ol*
DIBAL (1M in hexane, 10ml) was added to a cold (−78°), stirred solution of Intermediate 5 (2.7g) in CH_2Cl_2 (50ml). After 2h a further quantity of DIBAL (6.7ml) was added and stirring

continued for 2.5h. MeOH (20ml) was added dropwise and after 15 min at room temperature ether (60ml) was added. The resultant mixture was filtered through hyflo and the filtrate evaporated to give the *title compound* as a gum (2.6g). I.r. ($CHBr_3$) 3580, 2720, 1718cm^{-1}

Intermediate 17
[1S-[1α,2β(S),3α,5α]]-3-Hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-(phenylmethoxy)cyclopentanepropanal*
To a cold (0°) solution of potassium *tert*-butoxide (2.9g) in THF (40ml), under N_2, was added (methoxymethyl)triphenylphosphonium chloride (8.84g). After 5 min a solution of Intermediate 16 (2.6g) in THF (25ml) was added and the mixture stirred at 0° for 30 min. A saturated solution of NH_4Cl (50ml) was added and the mixture was extracted with ER (3×60ml). The combined extracts were dried and evaporated to yield an oil (9.1g).
The crude product was stirred in 1:1 0.25N sulphuric acid—acetone (80ml) for 48h at ambient temperature. The organic solvent was then removed *in vacuo* and the aqueous residue extracted with EA (3×50ml). The combined organic phases were washed with saturated brine (30ml), dried and evaporated. The residue was purified by chromatography using ER as eluent to give the *title compound* as an oil (1.5g).
I.r. ($CHBr_3$) 3580, 3460, 2720, 1718cm^{-1}.

Intermediate 18
[1S-[1α,2β(2S),3α,5α]]-2-[3-Phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-5-(phenylmethoxy)-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentanepropanal*
Dihydropyran (0.95ml) and pyridinium toluene-p-sulphonate (0.1g) were added to a stirred solution of Intermediate 17 (1.44g) in CH_2Cl_2 (40ml) at 0°. After stirring for 20h at room temperature the mixture was washed with water (2×10ml), 8% $NaHCO_3$ (2×10ml) and brine (2×10ml). The solvent was evaporated and the residue purified by chromatography using 1:1 ER-PE (40–60°) as eluent to yield the *title compound* as a gum (1.9g). I.r. ($CHBr_3$) 2720, 1720cm^{-1}.

Intermediate 19
[4aR-[4aα,5α(2R),6β,7aα]]-Octahydro-5-[3-phenoxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]propoxy]-6-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopenta[b]pyran-2-ol*
A solution of Intermediate 18 (0.94g) in EA (50ml) was hydrogenated over pre-reduced 10% palladium on charcoal (0.97g) at N.I.P. for 22h. The catalyst and solvent were removed and the residual oil (0.75g) purified by chromatography using 3:1 ER-PE (40–60°) as eluent to give the *title compound* as an oil (0.49g).
I.r. ($CHBr_3$) 3570cm^{-1}
In the following examples, where the experimental details are not given, the compounds were prepared in a similar manner to the compound of Example 1.

Example 1
[1R-[1α(Z),2β(R),3α]]-(−)-4-Acetylphenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate*
A solution of Intermediate 11a (0.24g) in 20:10:3 acetic acid-water-THF (2.5ml) was heated at 40° for 4h. The solvent was removed *in vacuo* and the residue purified by chromatography on acid-washed (pH3.8) silica using 75:1 ER-MeOH as eluent to give the *title compound* as a white solid (0.14g), m.p. 55–56.5°. Crystallisation from methyl acetate-PE gave a white solid, m.p. 64–65°, $[\alpha]_D^{22.4}$ −18.1° (MeOH)
Analysis Found: C,68.02; H,6.63.
$C_{29}H_{34}O_8$ requires C,68.22; H,6.71%.

Example 2
[1R-[1α(Z),2β(R),3α]]-(−)-4-(Acetylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate*
A solution of Intermediate 11b (0.3g) in 20:10:3 acetic acid-water-THF (3ml) was heated at 40–43° for 4h. The solvent was removed *in vacuo* and the residue purified by chromatography on acid-washed (pH 3.8) silica using EA as eluent to give the *title compound* as a white solid (0.12g), m.p. 60–63°. Crystallisation from t-butylmethylether gave a white solid, m.p. 74.5–75°. $[\alpha]_D^{20.9}$ −19.4° (MeOH)
Analysis Found: C,65.86; H,6.71; N,2.66.
$C_{29}H_{35}NO_8$ requires C,66.27; H,6.71; N,2.57%.

Example 3
[1R-[1α(Z),2β(R),3α]]-4-[(Aminocarbonyl)amino]phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate,* (0.04g) from Intermediate 11c (0.09g) purified using 20:1 EA-MeOH as eluent. T.l.c. 20:1 EA-MeOH Rf 0.25. I.r. ($CHBr_3$) 3570, 3500, 3400, 1740, 1680cm^{-1}

Example 4
[1R-[1α(Z),2β(R),3α]]-(−)-4-(Benzoylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate*
A solution of Intermediate 11d (0.24g) in 20:10:3 acetic acid-water-THF (3ml) was heated at 40–42° for 3H. The solvent was removed *in vacuo* and the residue purified by chromatography on acid-washed (pH 3.8) silica using 7:3 EA-cyclohexane as eluent to give after trituration with ER the *title compound* as a white powder (0.07g), m.p. 125–127°. $[\alpha]_D^{20}$ −29.3° ($CHCl_3$)
Analysis Found: C,69.4; H,6.4; N,2.3.
$C_{34}H_{37}NO_8$ C,69.5; H,6.4; N,2.4%.

Example 5
[1R-[1α(Z),2β(R),3α]]-(−)-4-[4-(Acetylamino)benzoylamino]phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate*
A solution of Intermediate 11e (0.24g) in 20:10:3 acetic acid-water-THF (3ml) was heated at 40–42° for 4h. The solvent was removed *in vacuo* to give a solid residue which was purified by chromatography on acid-washed (pH3.8) silica using EA as eluent to give after trituration with ER the *title compound* as a white powder (0.06g), m.p. 150–154°, $[\alpha]_D^{20}$ −10° (MeOH)
Analysis Found: C,66.7; H,6.3; N,4.5.
$C_{36}H_{40}N_2O_9$ requires C,67.1; H,6.3; N,4.4%.

Example 6
[1R-[1α(Z),2β(R),3α]]-(−)-4-(Aminocarbonyl)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate*
A solution of Intermediate 11f (0.44g) in 20:10:3 acetic acid-water-THF (5ml) was heated at 40° for 3h. The solvent was removed *in vacuo* and the residue purified by chromatography on acid-washed (pH3.8) silica using 95:5 EA-EtOH as eluent. Trituration with ER followed by crystallisation from EA-PE gave the *title compound* as a white solid (0.14g), m.p. 104–105°, $[\alpha]_D^{20}$ −13.2° (EtOH)
Analysis Found: C,65.65; H,6.7; N,2.7.
$C_{28}H_{33}NO_8$ requires C,65.7; H,6.5; N,2.7%.

Example 7
[1R-[1α(Z,S),2β(R*),3α]]-(+)-4-[2-(Acetylamino)-3-amino-3-oxopropyl]phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate*
A solution of Intermediate 11g (0.37g) in 20:10:3 acetic acid-water-THF (6ml) was heated at 40° for 3h. The solvent was removed *in vacuo* and a portion of the residue (0.19g) was purified by chromatography on acid-washed (pH3.8) silica gel using 9:1 CH_2Cl_2-EtOH as eluent. Trituration with ER followed by crystallisation from EA-PE gave the *title compound* as a white solid (0.04g), m.p. 105°
$[\alpha]_D^{20}$ +3.5° (EtOH), I.r. (Nujol) 1740, 1720, 1660, 1645cm $^{-1}$.

Example 8
[1R-[1α(Z),2β(R),3α]]-(−)-3-(Benzoylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate*
A solution of Intermediate 11h (0.35g) in 20:10:3 acetic acid-water-THF (5ml) was heated at 40–42° for 2.5h. The solvent was removed *in vacuo* and the residue purified by chromatography on acid-washed (pH 3.8) silica using 3:1 EA-cyclohexane as eluent to give after trituration with ER the *title compound* as a white powder (0.16g), m.p. 89–91°, $[\alpha]_D^{20}$ −25.7° ($CHCl_3$)
Analysis Found: C,69.3; H,6.4; N,2.2.
$C_{34}H_{37}NO_8$ C,69.5; H,6.4; N,2.4%.

Example 9
[1R-[1α(Z),2β(R),3α]]-(−)-4-(N,N-Dimethylaminocarbonyl)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate,* (0.08g) from Intermediate 11i (0.24g) purified using EA as eluent. I.r. ($CHBr_3$) 3580, 3420, 1745, 1624cm $^{-1}$, $[\alpha]_D^{20}$ −29° ($CHCl_3$)
Analysis Found: C,66.53; H,7.04; N,2.53.
$C_{30}H_{37}NO_8$ requires C,66.77; H,6.91; N,2.60%.

Example 10
[1R-[1α(Z),2β(R),3α]]-(−) Methyl 4-[[7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-1-oxo-5-heptenyl]oxy]benzoate*
A solution of Intermediate 11i (0.19g) in 20:10:3 acetic acid-water-THF (10ml) was heated at 40° for 3h. The solvent was removed *in vacuo* and the residue purified by chromatography on acid-washed (pH 3.8) silica using ER as eluent to give the *title compound* as a white solid (0.1g), m.p. 45–47°, $[\alpha]_D^{20}$ −33° ($CHCl_3$)

Analysis Found: C,66.25; H,6.63.
$C_{29}H_{34}O_9$ requires C,66.15; H,6.51%

Example 11
[1R-[1α(Z),2β(R),3α]]-(−)-4-[4-(Hydroxy)benzoylamino]phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate*
A solution of Intermediate 11k (0.57g) in 20:10:3 acetic acid-water-THF (10ml) was heated at 40° for 3.5h. The solvent was removed *in vacuo* and the residue was purified by chromatography on acid-washed (pH3.8) silica using 4:1 EA-PE as eluent to give after trituration with ER a white powder (0.22g). Crystallisation from EA-PE gave the *title compound* as a white solid (0.18g), m.p. 108–110° $[\alpha]_D^{20}$ −13.9° (EtOH)
Analysis Found: C,67.35; H,6.1; N,2.2.
$C_{34}H_{37}NO_9$ requires C,67.65; H,6.2; N,2.3%.

Example 12
[1R-[1α(Z),2β(R),3α]]-2-(Benzoylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate,* (0.029g) from Intermediate 11l (0.050g) purified using 2:1 EA-cyclohexane as eluent. T.l.c. 2:1 EA-cyclohexane Rf 0.2, I.r. ($CHBr_3$) 3580, 3440, 1742, 1675cm^{-1}

Example 13
[1R-[1α(Z),2β(R),3α]]-2-Naphthalenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate*
A solution of Intermediate 11m (0.44g) in 20:10:3 acetic acid-water-THF (12ml) was heated at 40–42° for 3h. The solvent was removed *in vacuo* and the residue was purified by chromatography on acid-washed (pH3.8) silica using 3:1 ER-EA as eluent to give after trituration with ER the *title compound* as a white powder (0.15g), m.p. 71–73°. $[\alpha]_D^{20}$ −35° ($CHCl_3$)
Analysis Found: C,71.79; H,6.60.
$C_{31}H_{34}O_7$ requires C,71.79; H,6.61%.

Example 14
[1R-[1α(Z),2β,3α]]-(−)-4-(Benzoylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate, (0.06g) from Intermediate 11n (0.11g) purified using ER as eluent. I.r. ($CHBr_3$) 3580, 3420, 1742, 1672cm^{-1}, $[\alpha]_D^{20}$ −7° (MeOH)
Analysis Found: C,69.42; H,6.85; N,2.21.
$C_{35}H_{39}NO_8$ requires C,69.87; H,6.53; N,2.3%.

Example 15
[1R-[1α(Z),2β,3α]]-4-Methoxyphenyl 7-[2-[3-(4-fluorophenoxy)-2-hydroxypropoxy]-3-hydroxy-5-oxocyclopentyl]-5-heptenoate, (0.06g) from Intermediate 11o (0.09g) purified using 97:3 ER-MeOH as eluent. I.r. ($CHBr_3$) 3580, 3450, 1745cm^{-1}
Analysis Found: C,64.75; H,6.59.
$C_{28}H_{33}FO_8$ requires C,65.10; H,6.44%.

Example 16
[1R-[1α(Z),2β,3α]]-4-(Methylthio)phenyl 7-[2-[3-(4-chlorophenoxy)-2-hydroxyproxy]-3-hydroxy-5-oxocyclopentyl]-5-heptenoate, 0.1g) from Intermediate 11p (0.16g) purified using 98:2 ER-MeOH as eluent. I.r. ($CHBr_3$) 3580, 3440, 1742cm^{-1}, T.l.c. 98:2 ER-MeOH Rf 0.25

Example 17
[1R-[1α(Z),2β,3α]]-4-(Methylsulphonyl)phenyl 7-[3-hydroxy-2-[2-hydroxy-3-[4-(methylthio)phenoxy]-propoxy]-5-oxocyclopentyl]-5-heptenoate
A solution of Intermediate 11q (0.14g) in 20:10:3 acetic acid-water-THF (3ml) was heated at 40–42° for 3h. The solvent was removed *in vacuo* and the residue was purified by chromatography on acid-washed (pH3.8) silica using 75:25 increasing to 90:10 EA-ER as eluent to give the *title compound* as a white solid (0.09g), m.p. 73–76°
I.r. ($CHBr_3$) 3580, 3440, 1742cm^{-1}

Example 18
[1R-(1α,2β(R),3α)]]-(−)-4-(Aminocarbonyl)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-4,5-heptadienoate,* (0.19g) from Intermediate 11r (0.35g) purified using 3:2 EA-CH_3CN as eluent. T.l.c. 3:2 EA-CH_3CN Rf 0.3, I.r. ($CHBr_3$) 3580, 3520, 3400, 1960, 1740, 1672cm^{-1}, $[\alpha]_D^{20}$ −21.0° $CHCl_3$)

Example 19
[1R-[1α(Z),2β(R),3α]]-(−)-4-(Benzoylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-*

oxocyclopentyl]-4-heptenoate
A solution of Intermediate 11s (0.17g) in 20:10:3 acetic acid-water-THF (10ml) was heated at 40° for 2h. The solvent was removed *in vacuo* and the residue purified by chromatography on acid-washed (pH 3.8) silica using 2:1 EA-cyclohexane as eluent to give the *title compound* as a solid (0.11g), m.p. 85–88°
I.r. ($CHBr_3$) 3580, 3430, 1745, 1675, $[\alpha]_D^{20}$ −27° ($CHCl_3$)

Example 20
[1R-[1α(Z),2β(R),3α]]-(−)-4-(Benzoylamino)phenyl 9-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-7-nonenoate*
A solution of Intermediate 11t (0.55g) in 20:10:3 acetic acid-water-THF (15ml) was heated at 40° for 4h. The solvent was removed *in vacuo* and the residue purified by chromatography on acid-washed (pH 3.8) silica using 7:3 EA:cyclohexane as eluent to give after trituration with ER the *title compound* as a white solid (0.24g), m.p. 121–122° $[\alpha]_D^{20}$ −34° ($CHCl_3$)
Analysis Found: C,70.23; H,6.66; N,2.17.
$C_{36}H_{41}NO_8$ requires C,70.22; H,6.71; N,2.27%.

Example 21
[1R-[1α,2β(R),3α]]-(−)-4-(Benzoylamino)phenyl 3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentaneheptanoate*
A solution of the compound of Example 4 (0.1g) in EA (35ml) was hydrogenated over pre-reduced 10% palladium on charcoal (0.03g) at N.T.P. for 40 min and then the solvent and catalyst were removed. The *title compound* was obtained as a white solid (0.07g), m.p. 127–130°, $[\alpha]_D^{20}$ −29.3° ($CHCl_3$)
Analysis Found: C,69.38; H,6.69; N,2.15.
$C_{34}H_{39}NO_8$ requires C,69.25; H,6.67; N,2.38%.

Example 22
[1R-[1α(E),2β(R),3α]]-(−)-4-(Aminocarbonyl)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate*
A solution of the compound of Example 6 (0.15g), thiophenol (0.46ml) and azobisisobutyronitrile (0.1g) in CH_2CN (3ml) and benzene (3ml) was stirred at reflux for 6.5h. Purification by chromatography (×2) on acid-washed (pH3.8) silica using 9:1 EA-CH_3CN as eluent gave the *title compound* as a gum (0.13g).
I.r. ($CHBr_3$) 3580, 3515, 3400, 1742, 1672cm $^{-1}$, $[\alpha]_D^{20}$ −30° ($CHCl_3$)
Analysis Found: C,66.12; H,6.8; N,2.52.
$C_{28}H_{33}NO_8$ requires C,65.74; H,6.5; N,2.74%.

Example 23
[1R-[1α(Z),2β(R),3α]]-(−)-4-(Benzoylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate*
Pivaloyl chloride (0.01ml) was added to a solution of Intermediate 1 (0.03g) and Et_3N (0.01ml) in dry DMF (1ml) at 0°. After 10 min a solution of 4-(benzoylamino)phenol (0.17g) and Et_3N (0.01ml) in DMF (1ml) was added and stirring continued for 2h at 0° and 3.5h at room temperature. The reaction mixture was diluted with EA (30ml) and washed consecutively with water (10ml), 10% copper sulphate solution (15ml), water (10ml) and brine (15ml). The dried organic extract was evaporated to give a residue which was purified by chromatography on acid-washed (pH3.8) silica using 1:1 cyclohexane-EA as eluent. The *title compound* was obtained as a white solid (0.05g).
I.r. ($CHBr_3$) 3580, 3430, 1745, 1675cm $^{-1}$, T.l.c. 1:1 Cyclohexane-EA Rf 0.15
The following are examples of pharmaceutical formulations using compounds of the invention. In the examples, the term "active ingredient" is used to denote a compound of the invention, such as a compound described in the preceding examples, for example the compound of Example 4.

1. Tablets
These may be prepared by direct compression

	mg/tablet
Active Ingredient	0.015 to 0.2
Magnesium stearate, BP	1.5
Microcrystalline cellulose, USP to compression weight	150.0

The active ingredient is blended with about 10% of the microcrystalline cellulose then blended with the remaining microcrystalline cellulose and magnesium stearate. The blend is then compressed using 6mm diameter punches into tablets on a suitable machine.
The tablets may be film coated with suitable film forming materials e.g. methyl cellulose or hydroxypropyl methylcellulose using standard techniques.

2. Capsules

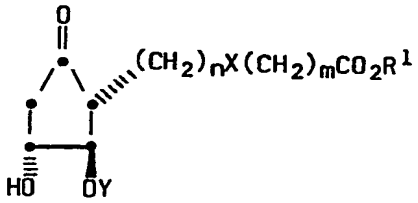
	mg/tablet
Active ingredient	0.015 to 0.2
Magnesium stearate, BP	1.0
*Starch 1500	100.0
to fill weight	

*A form of directly compressible starch.

The active ingredient is preblended with some of the Starch 1500 then this preblend is mixed with the remaining Starch 1500 and magnesium stearate. The mix is then filled into size No 2 hard gelatin capsule shells using suitable machinery.

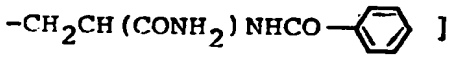
CLAIMS

1. Compounds of the general formula (I)

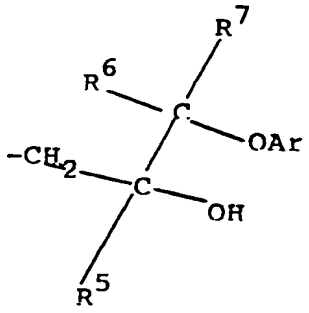


(1)

wherein
n is 1 or 2;
m is 2–5 and X is cis or trans –CH=CH– or $-CH_2CH_2-$; or m is 1–4 and X is –CH=C=CH–;
R' is
(a) phenyl [optionally substituted by C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, methylthio, methylsulphinyl, methylsulphonyl, halogen, $-CO_2R^2$ [where R^2 is a hydrogen atom or C_{1-4} alkyl or phenyl], $-NHCOR^2$ [where R^2 is as defined above or is a phenyl group optionally substituted by hydroxyl, CH_3CONH- or benzoylamino], $-CONR^3R^4$ [where R^3 and R^4 may be the same or different and are each a hydrogen atom or C_{1-4} alkyl group], $-NHCONH_2$, $-CH_2CH(CONH_2)NHCOCH_3$, or



(b) 2-naphthyl;
Y is



where R^5, R^6 and R^7 are each a hydrogen atom or a methyl group and at least one is a hydrogen atom, and

Ar is a phenyl group (optionally substituted by one or two C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkythio, C_{1-4} alkylsulphinyl, C_{1-4} alkylsulphonyl, halogen or trifluoromethyl groups)
and the salts of compounds in which R^2 is a hydrogen atom.

2. Compounds as claimed in claim 1 in which X is $-CH=CH-$ or $-CH_2-CH_2-$ and m is 3 when n is 1 and m is 2 or 4 when n is 2; or X is $-CH=C=CH-$ and m is 2 when n is 1 and m is 1 or 3 when n is 2.

3. Compounds as claimed in claim 1 or claim 2 in which R^1 is phenyl substituted by a C_{1-4} alkoxy, C_{1-4} alkanoyl, methylthio, methylsulphonyl, $-CO_2R^2$, $-NHCOR^2$, $-CONR^3R^4$, $-NHCONH_2$ or $-CH_2CH(CONH_2)NHCOCH_3$ group or R^1 is a 2-naphthyl group.

4. Compounds as claimed in claim 1 or claim 2 in which R^1 is phenyl substituted by a methoxy, acetyl, $-CO_2CH_3$, $-NHCOCH_3$, benzoylamino, $-CONH_2$, $-CON(CH_3)_2$ or $-CH_2CH(CONH_2)NHCOCH_3$ group, or R^1 is a 2-naphthyl group.

5. Compounds as claimed in any preceding claim in which R^5, R^6 and R^7 are hydrogen atoms and Ar is phenyl or phenyl substituted by fluoro or chloro.

6. Compounds as claimed in claim 1 in which:
X is $-CH=CH-$ or $-CH_2CH_2-$ and n is 1 and m is 3 or n is 2 and m is 2 or 4, or X is $-CH=C=CH-$ and n is 1 and m is 2 or n is 2 and m is 1 or 3;
R^1 is a phenyl group substituted by a methoxy, acetyl, $-CO_2CH_3$, $-NHCOCH_3$, benzoylamino, $-CONH_2$, $-CON(CH_3)_2$ or $-CH_2CH(CONH_2)NHCOCH_3$ group or R^1 is a 2-naphthyl group;
R^5 is a hydrogen atom or a methyl group;
R^6 and R^7 are hydrogen atoms; and
Ar is a phenyl or phenyl substituted by fluoro or chloro.

7. Compounds as claimed in any preceding claim in which the carbon atom carrying the group $-(CH_2)_nX(CH_2)_mCO_2R^1$ is in the R-configuration.

8. A compound as claimed in claim 1 said compound being:
[1*R*-[1α(*Z*),2β(R*),3α]]-(−)-4-(Benzoylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate.

9. A compound as claimed in claim 1, said compound being:
[1*R*-[1α(*Z*),2β(R*),3α]]-(−)-4-(Acetylphenyl) 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(R*),3α]]-(−)-4-(Acetylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*,*S**),2β(*R**),3α]]-(+)-4-[2-(Acetylamino)-3-amino-3-oxopropyl]phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(R*),3α]]-(−)-4-(Aminocarbonyl)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(R*),3α]]-(−)-3-(Benzoylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(R*),3α]]-(−)-4-(N,N-Dimethylaminocarbonyl)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(R*),3α]]-(−) Methyl 4-[[7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-1-oxo-5-heptenyl]oxy]benzoate;
[1*R*-[1α(*Z*),2β(R*),3α]]-2-Naphthalenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(Z),2β,3α]]-(−)-4-(Benzoylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-2-methyl-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β,3α]]-4-Methoxyphenyl 7-[2-[3-(4-fluorophenoxy)-2-hydroxypropoxy]-3-hydroxy-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(R*),3α]]-(−)-4-(Benzoylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-4-heptenoate;
[1*R*-[1α,2β(R*),3α]]-(−)-4-(Benzoylamino)phenyl 3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentaneheptanoate; or
[1*R*-[1α(*E*),2β(R*),3α]]-(−)-4-(Aminocarbonyl)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate.

10. A compound as claimed in claim 1, said compound being:
[1*R*-[1α(*Z*),2β(R*),3α]]-(−)-4-[4-(Acetylamino)benzoylamino]phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β(R*),3α]]-2-(Benzoylamino)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-5-heptenoate;
[1*R*-[1α(*Z*),2β,3α]]-4-(Methylsulphonyl)phenyl 7-[3-hydroxy-2-(2-hydroxy-3-(4-methylthio)phenoxy-]propoxy]-5-oxocyclopentyl]-5-heptenoate; or
[1*R*-[1α(*Z*),2β,3α]]-(−)-4-(Benzoylamino)phenyl 9-[3-hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-7-nonenoate.

11. A pharmaceutical composition comprising a compound as claimed in any preceding claim together with one or more pharmaceutical carriers.

12. A composition as claimed in claim 11 in the form of a tablet.

13. A composition as claimed in claim 11 in the form of a tablet containing the compound of claim 8 as active ingredient.

14. A composition as claimed in claim 11 in the form of a tablet containing 0.015 to 0.2 mg of the compound of claim 8.

15. A process for the preparation of a compound as claimed in claim 1 which comprises:

(a) deprotecting a corresponding compound in which the ring hydroxy group and the hydroxy group in Y are protected;

(b) esterifying a corresponding compound in which R^1 is a hydrogen atom;

(c) in the preparation of a compound in which X is $-CH_2-CH_2-$, reducing a corresponding compound in which X is $-CH=CH-$ or an acetylene group;

(d) in the preparation of a compound in which X is $-CH=CH-$, selectively reducing the corresponding compound in which X is an acetylene group; or

(e) in the preparation of a compound in which X is trans $-CH=CH-$, isomerising the corresponding compound in which X is cis $-CH=CH-$.

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